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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,302	09/26/2003	Hong Jin	NS210US	4464

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,302	JIN ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,13,21-44,46,55,58-60 and 241-250* is/are pending in the application.

4a) Of the above claim(s) *3,13, 58-60 and 21-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,55 and 241-250* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections/objections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 46, 55 and 241-250 are examined on the merits. Claims 3, 13, 21-44 and 58-60 remain withdrawn since they are drawn to non-elected inventions.

Response to Arguments

Applicant's arguments with respect to claims 46, 55 and 241-250 have been considered but are moot in view of the new ground(s) of rejection. However, some prior cited publications have been referenced below with responses to arguments.

Response to Amendment

The declaration under 37 CFR 1.132 filed February 4, 2008 is sufficient to overcome the rejection of claims 46, 55 and 241-247 based upon 35 U.S.C. 102(a) as being anticipated by Lu et al. (Journal of Virology, 2002).

Inventorship

In view of the papers filed February 4, 2008, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by deleting the following inventors: Xing Cheng and Helen Zhou, while retaining Bin Lu and Hong Jin as co-inventors with the newly added inventor, Robert Brazas.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 102

(New Rejection Necessitated by Amendments) Claim 46, 241-244 and 247 are rejected under 35 U.S.C. 102(b) as being anticipated by Caravokyri et al. (Journal of General Virology, 1992).

The claimed invention is drawn to an isolated nucleic acid encoding a replicating recombinant respiratory syncytial virus of subgroup A (RSV) with an attenuated phenotype and comprises a phosophoprotein (P) with one mutated amino acid residue. The altered amino acid residue is located at positions 172, 174, 175 or 176 of the P protein.

Caravokyri et al. teach the passaging of wild-type, temperature sensitive and a mutant A and B subgroup RSV in BS-C-1 cells. Caravokyri et al. sequenced the viral isolates and determined that position 172 contained a residue mutation in virus *ts*N19 cultures. In addition, Caravokyri et al. observed similar viral titers between the temperature sensitive virus and that of the wild type.

Claim Rejections - 35 USC § 103

Claims 248-250 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caravokyri et al. as applied to claims 46 and 241-247 above, and further in view of Krempl et al. (US PGPub 2002/0146433 A1), Khattar et al. (Journal of General Virology, 2001), Genbank Accession # M74568 (1993) and Girault (Encyclopedia of Molecular Biology, 1999).

The instant invention is drawn to an immunologically effective amount of a live attenuated recombinant respiratory syncytial virus of subgroup A (RSV) with an attenuated phenotype and comprises a phosophoprotein (P) with one mutated or substituted amino acid residue. The altered amino acid residue is located at positions 172, 174, 175 or 176 or 172 and 176 of the P protein and this alteration eliminates a phosphorylation site. The instant invention is also drawn to the nucleic acid, which encodes the RSV of the instant invention.

The teachings of Caravokyri et al. are discussed above, however, they do not teach mutations/substitutions at positions 174, 175 or 176 or 172 and 176.

Krempl et al. teach modifying the various proteins/genes of RSV in order to develop a desired phenotype of from a wild-type virus. Krempl et al. suggest the use of either complete or partial mutations/substitutions/deletions of the P protein, L protein, M protein, etc.

Khattar et al. teach the essential interaction of Bovine RSV P protein and Nucleoprotein (N) in viral replication. Khattar et al. examined the effects of various deletions on the P protein's interaction with the Nucleoprotein and observed a dissociated interaction when amino acid regions 161-180 or 221-241 of the P protein were deleted (see figure 3A).

The Genbank Accession #M74568 provides the complete genome of Human Respiratory syncytial virus of a subgroup A isolate with the P gene located between bases 2329-3242.

Girault teaches the ubiquitous involvement of protein phosphorylation and protein activity or protein-protein interactions. Several amino acids can be phosphorylated (see table 1). Based on the teachings of Girault, 10 of 20 residues between the 161-180 amino acid range of Bovine RSV P protein, as taught by Khattar et al. above, can be altered by phosphorylation. These positions are 161, 163, 164, 167, 168, 174, 175, 176 and 179.

It would have been obvious to one of ordinary skill in the art to modify the composition taught by Caravokyri et al and Krempl et al. in order to obtain an immunogenic recombinant RSV of subgroup A with an amino acid substitution at position 176 along with position 172, thereby generating an attenuated RSV. One would have been motivated to do so, given the suggestion by Caravokyri et al. that the amino acid substitution at position 172 results in a temperature-sensitive, recombinant RSV and that Krempl et al. suggest modifying the RSV proteins, including the phosphoprotein, by either partial or complete mutation/deletion/substitution. There would have been a reasonable expectation of success, given the knowledge that the interaction of the P protein and nucleoprotein of Bovine RSV is interrupted by deleting amino acids 161-180, as taught by Khattar et al., also given the knowledge that phosphorylation of amino acids that are located within the 161-180 amino acid region of the P protein can interfere with protein-protein interactions in addition to the knowledge that the amino acids discussed in table 1 provide guidance for residues that do or don't contain phosphorylation sites, as taught by Girault et al., and also given the knowledge that the complete genome of a RSV subgroup A virus was known prior to that of the claimed invention as disclosed by the Genbank Accession. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to arguments:

Applicants argue that Khattar et al. do not teach a replicating, attenuated RSV. In response, this is not disputed, however, the research of Khattar et al. reveals the regions of RSV's phosphoprotein that are necessary for nucleoprotein-P protein interaction, thereby

providing further guidance towards targeting specific residues, such as 161, 163, 164, 167, 168, 174, 175, 176 and 179 of the P protein.

Applicants argue that Girault et al. do not talk about RSV. This is acknowledged, however, the teachings of Girault et al. reveal how one skilled in the art can modify phosphorylation sites by changing amino acid residues based on the information from table 1, thereby either removing or inserting a phosphorylation site into proteins involved/affected by phosphorylation events.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(New Rejection) Claim 55 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition containing a respiratory syncytial virus containing mutations in the phosphoprotein (P), does not reasonably provide enablement for a respiratory syncytial virus vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The claimed invention is to a live, attenuated respiratory syncytial virus vaccine comprising a virus with an amino acid mutation in the P protein of the virus. However, no working examples are presented in the specification towards directing one skilled in the art that such a vaccine was produced. Furthermore, the state of the does not recognize such a vaccine as evidenced by Meyer et al. (Comparative Immunology, Microbiology and Infectious Diseases, 2008) and Power (Journal of Clinical Virology, 2008). In particular, Meyer et al. teach that while several vaccine candidates have been tried over time, none have achieved promising results. This is further complicated since a reliable animal model doesn't exist. Power also teaches that no vaccine is recognized for RSV and that during viral infection, it is capable of evading host immune reactions due to its low immunogenecity. Therefore, additional experimentation is required for determining what formulation of RSV is capable of vaccinating a host against RSV given its unpredictable background thus far. For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed product.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46, 55 and 241-260 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 46 recites, "…which phosphoprotein comprises at least one mutated amino acid residue.", however, without an amino acid sequence to refer to, it is unclear what is defined by a "mutation" since it can be construed that one amino acid sequence is a mutation of any other amino acid sequence.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN P BLUMEL/
Examiner
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/Bruce Campell/
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